Conferences and Reviews

Initial Manifestation of Primary Hyperoxaluria Type I in Adults

Recognition, Diagnosis, and Management

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Primary hyperoxaluria type I may initially manifest as urolithiasis, renal insufficiency, or symptoms of systemic oxalosis. This hereditary disorder was fatal until effective therapies evolved during the past two decades. Difficulty in recognizing and diagnosing this disorder in adults is illustrated in a report of a patient eventually restored to good health by high-flux dialysis and combined renal and hepatic transplantation. I explore the molecular processes of the genetic defect and discuss clinical indicators of primary hyperoxaluria type I, manifestations of oxalosis, the pathogenesis of chronic oxalate nephropathy, and the diagnosis and management of this disease.

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An autosomal recessive inborn error of glyoxylate metabolism, primary hyperoxaluria type I, can be cured by combined hepatic and renal transplantation.[1,2] The rarity of this disorder and its usual presentation in childhood ensure that physicians practicing adult medicine will be unlikely to be called on to diagnose the disorder in 1 of an estimated 65 new patients presenting annually in the United States.[3] The variability of initial clinical manifestations and the difficulty in accessing confirming studies for a patient whose condition is undiagnosed before renal failure develops complicate the management of this curable disorder. This review aids in the recognition, diagnosis, and treatment of patients who initially manifest primary hyperoxaluria type I as adults.*

Pathogenesis

Severe deficiency of enzyme activity catalyzing the transamination of glyoxylate to glycine (Figure 1) allows an overproduction of oxalate. In at least 75% of patients with primary hyperoxaluria type I, this overproduction is accompanied by excessive synthesis of glycolate (a valuable marker of this disorder).[4] Patients with primary hyperoxaluria generate oxalate at rates three to ten times normal.[5-7] Oxalate is not further metabolized; instead, renal excretion is required to prevent oxalosis, the accumulation of the highly insoluble calcium salt of oxalate in extrarenal tissues. Sustained hyperoxaluria leads to extreme supersaturation of urine with calcium oxalate, to calculi formation potentially complicated by urinary tract obstruction or infection, to renal tubulointerstitial injury and nephrocalcinosis, and to impaired renal function. In patients with this disorder, a decline in renal function from any cause forces the excretion of excessive oxalate by a diminishing number of nephrons, which may magnify oxalate-induced nephrotoxicity. A systemic accumulation of oxalate begins with glomerular filtration rates (GFRs) of less than 60 ml per minute.[5] With a decline in the GFR to 25 to 30 ml per minute or less, plasma oxalate levels rise dramatically, and generalized deposition of calcium oxalate accelerates.[5] Until the 1980s, the complications of urolithiasis, renal failure, and oxalosis led to death in 65% of these patients before age 5 years and in more than 80% before age 20.[1] The initial manifestation of the disease in adulthood has been unusual.

Investigations in the United Kingdom and the United States contributed greatly to the clinical and metabolic understanding of primary hyperoxaluria type I, which was first diagnosed in a living patient barely 40 years ago.[1,8] Elegant studies of the past eight years have defined the enzyme defect responsible for the disorder and its genetic and metabolic diversity.[4] This basic research has improved the diagnosis and treatment of this disorder dramatically. An extensively referenced review of its molecular processes has recently been published.[9]

Normally, to prevent the excessive production of relatively insoluble oxalate, a specific enzyme confined to hepatic peroxisomes, alanine-glyoxylate aminotransferase (AGT), effectively detoxifies glyoxylate by converting this metabolic intermediary to glycine. About

*See also the editorial by L. H. Smith, MD, "A Rare Twist to a Common Problem," on pages 83-84 of this issue.

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ABBREVIATIONS USED IN TEXT

AGT = alanine-glyoxylate aminotransferase
CT = computed tomographic
GFR = glomerular filtration rate

60% of patients with type I primary hyperoxaluria have no hepatic AGT activity. Immunochemical analyses of hepatic biopsy specimens suggest that the absence of AGT catalytic activity is usually accompanied by a loss of immunoreactivity of the inactive enzyme (group A, Table 1).[4] In a few patients, however (group B), the genetic mutation produces an immunologically detectable enzymatic protein devoid of AGT activity. About 40% of patients (group C) show considerable AGT activity, and many have AGT levels similar to those found in asymptomatic heterozygotes. The results of immunoelectron-microscopy indicate why adequate AGT catalytic activity results in an overproduction of oxalate: the enzyme is located in mitochondria instead of in peroxisomes, where glyoxylate can be metabolized efficiently. Thus, about 40% of patients with type I hyperoxaluria inherit a gene for active AGT that is functionally inert because it is located in the wrong organelle.

Pharmacologic dosing of the cofactor pyridoxine induces enough enzyme activity to shift the product of glyoxylate metabolism from oxalate to glycine in a small fraction of this subset of patients (4 of 24 group C patients in a series of 59 patients).[4] After cloning and sequencing the human AGT gene, point mutations were identified on chromosome 2 that are responsible for specific amino acid substitutions in the AGT molecule and that negate enzyme activity (group B), negate both enzyme activity and immunoreactivity (group A), or mistarget active enzyme to mitochondria (group C). A description of three patients with mutations that allow enzymatically inactive AGT to be located partially in

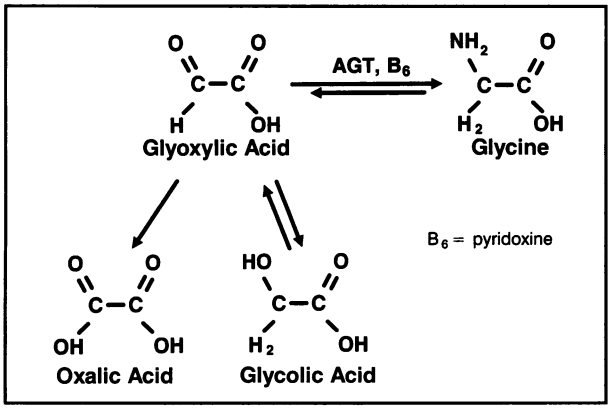

Figure 1.—The major pathways of glyoxylate metabolism are shown. Alanine-glyoxylate aminotransferase (**AGT**)-catalyzed transamination of glyoxylate to glycine and specific enzyme pathways converting glycolate and glycine to glyoxylate are confined to hepatic peroxisomes.

TABLE 1.—*Hepatic Alanine-Glyoxylate Aminotransferase (AGT) in Primary Hyperoxaluria Type I (PH-I)**

Group†	Approximate Percentage of PH-I Patients	Microassayable AGT Activity	Immunoreactive AGT Protein‡
A.....	40	–	–
B.....	20	–	+ (peroxisomes)
C.....	40	+	+ (mitochondria)

+ = present, – = absent

*From Danpure.[4]
†The designation of group A, B, and C patients facilitates discussion in the text.
‡The subcellular location of immunologically detectable AGT is indicated in parentheses.

mitochondria and partially in peroxisomal corelike structures implies that the phenotypic heterogeneity of this disorder is even more complex than Table 1 indicates.

Clinical Presentation

Typically, primary hyperoxaluria type I initially manifests in infancy or childhood as recurrent calcium oxalate urolithiasis, occasionally with insidious renal insufficiency or symptomatic oxalosis due to renal failure. Although 90% of patients with this disorder died within ten years of the development of the first symptom,[1] its diagnosis by pediatricians now allows prophylaxis that may preserve renal function and health.[3,8,10] A delay of diagnosis until adulthood despite substantial symptoms in childhood is relatively common, however.

Although unusual, the initial manifestation of symptoms in an adult aged 18 years or older was documented in 41 cases reported in the American and European biomedical literature in the past 40 years. Eight patients were in their fourth decade of life, one was in the fifth decade,[11] and five were in their sixth or seventh decade when the first symptom appeared.[4,12-14] The oldest patient appeared with arthralgia related to microcrystalline arthropathy, renal insufficiency, and nephrocalcinosis at age 66 years and died at age 71 after four years of dialysis.[14]

Report of a Case

The patient, a 45-year-old man, was seen in January 1991 because of morning nausea, a 2.3-kg (5-lb) weight loss, and muscle cramping of about five weeks. The medical history was uneventful except for episodes of dysuria and microscopic hematuria with negative culture results in November 1987 and again in February 1988. On both occasions, symptoms resolved without side effects during several days of treatment with the combination of sulfamethoxazole and trimethoprim. Follow-up urinalyses did not show hematuria. Studies done in April 1988 included a renal ultrasonogram, complete blood count, determinations of serum calcium, phosphorus, and parathyroid hormone levels, and an antinuclear antibody study, results for all of which were normal. A 24-hour urinary protein excretion was 0.05 grams (52 mg); serum creatinine levels ranged from 115 to 124 μmol per liter (1.3 to 1.4 mg per dl; versus 93 μmol per liter [1.05 mg per dl] in 1978). An extensive evaluation of symp-

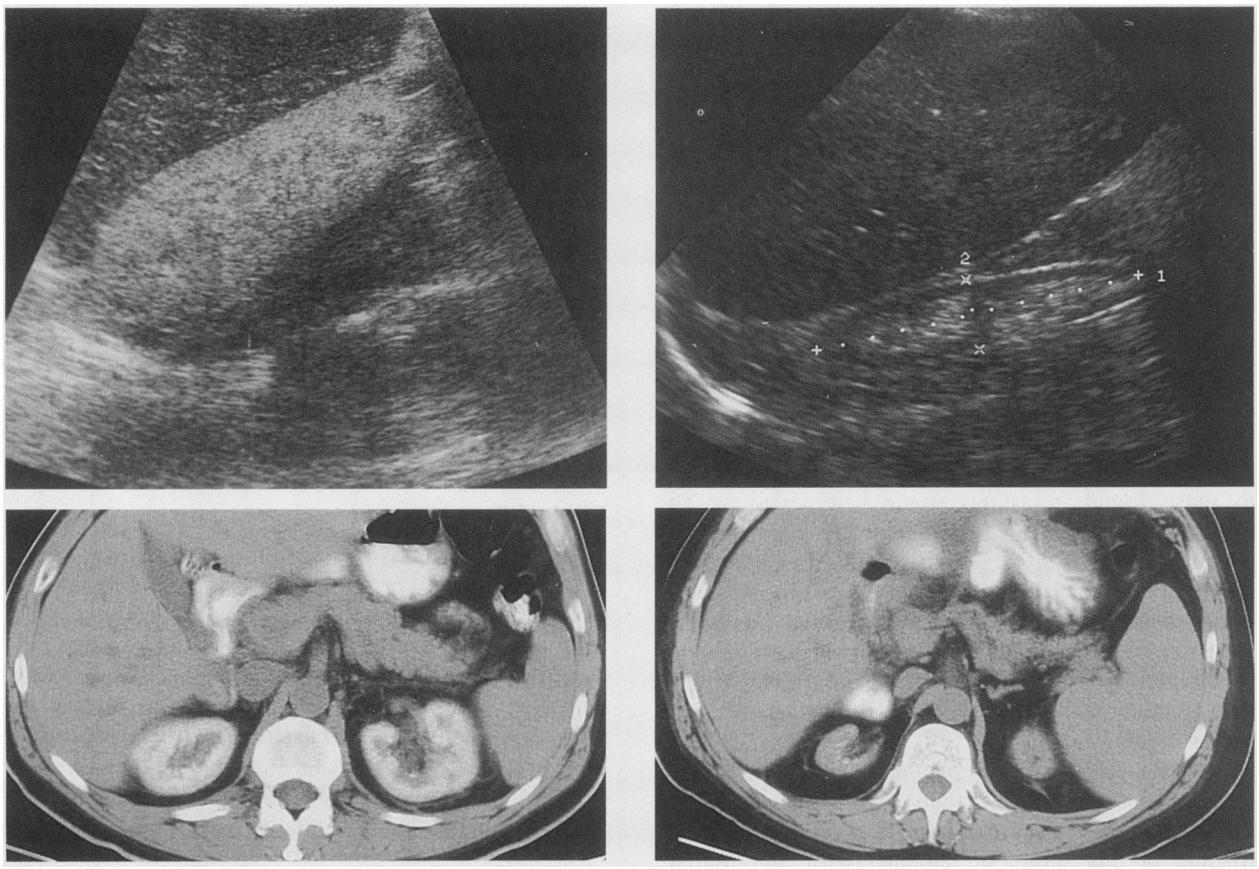

Figure 2.—Top left, A right renal ultrasonogram done in January 1991 showed the kidneys to be normal size and highly echogenic. **Top right,** A renal ultrasonogram done in December 1992 showed an atrophied right kidney with an echolucent cortex. **Bottom left,** Abdominal computed tomographic imaging without intravenous contrast was done in April 1991 and (**bottom right**) in August 1992. This imaging documented a reduction in renal cortical calcium oxalate deposition as well as renal atrophy after hepatic and renal transplantation in July 1991.

toms, medical history, habits, and possible toxic or infectious exposures proved unhelpful. The patient's three children and five siblings were healthy. His mother died at age 55 from complications of diabetes mellitus and hypertension and his father at age 84 of "old age." He was unaware of any family history of renal disease.

On physical examination, the results of which were normal except for azotemic fetor, the blood pressure was 130/90 mm of mercury with the patient either seated or standing. Laboratory data included the following: serum urea, 39.5 mmol per liter (blood urea nitrogen, 110 mg per dl); serum creatinine, 1,574 μmol per liter (17.8 mg per dl); mild metabolic acidosis; serum calcium, 2.32 mmol per liter (9.3 mg per dl); phosphorus, 2.62 mmol per liter (8.1 mg per dl); and hematocrit, 0.22 (21.9%). Urinalyses disclosed as many as 15 leukocytes and 20 erythrocytes per high-powered field, moderate calcium oxalate dihydrate crystalluria, and proteinuria (30 mg per dl; electrophoretically determined to be 16% albumin and 84% varied globulins without paraprotein). The kidneys on nephrosonography were found to be normal size and highly echogenic without corticomedullary demarcation or signs of obstruction (Figure 2). The results of other studies, including C3 and C4 serum complement, serum protein electrophoresis, liver function tests, chest x-ray films, and an electrocardiogram, were normal; the results of a tuberculin skin test and tests for antinuclear antibody, anti-DNA, and hepatitis B surface antigen were all negative. The intravenous administration of saline solution did not improve azotemic indices, prompting hemodialysis.

A surgical renal biopsy specimen four days after the recognition of nonoliguric azotemia in this clinically hydrated patient showed interstitial fibrosis and mononuclear cell infiltration (Figure 3). The pathologist recognized a few small crystalline deposits consistent with calcium oxalate scattered within tubular lumina and interstitium that were occasionally associated with small, multinucleated giant cells. Refractile crystalline material was not found, possibly because tissue was prepared in methacrylate resin instead of paraffin. Nonspecific, trace deposition of fluorescein-conjugated antisera within glomerular mesangium was not accompanied by immunofluorescence of tubular structures. Electron microscopy identified crystals with the needle-shaped morphologic features of calcium oxalate.

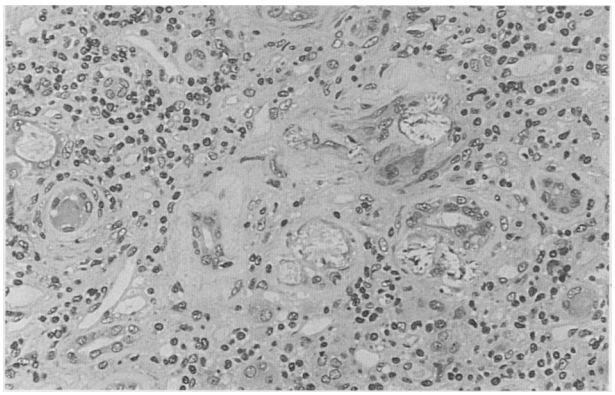

Figure 3.—A renal biopsy specimen shows chronic interstitial fibrosis and mononuclear cell infiltration. Crystals with morphologic features of calcium oxalate next to distorted tubules are sometimes surrounded by multinucleated giant cells (hematoxylin-eosin stain; original magnification, ×200).

Four urinalysis reports between 1974 and 1981 noted "4+ calcium oxalate crystals." Episodes of urethral discomfort and microscopic hematuria may have signaled the passage of small calculi. The diagnosis of primary hyperoxaluria type I was supported by later observations. The absence of diarrhea, steatorrhea, or an antecedent gastrointestinal surgical procedure and normal findings on gastric and small intestinal contrast radiography indicated that enteric hyperoxaluria was not present; the patient did not take vitamin C supplements, did not have exposure to ethylene glycol, and did not consume foods high in oxalate. Extreme, diffuse echogenicity and prominent radiographic and computed tomographic (CT) density of the normal-sized renal cortices suggested nephrocalcinosis. An abdominal x-ray film disclosed 3- and 5-mm calcific calculi in the lower pole of the left kidney.

The examination of a February 1991 biopsy specimen of the iliac crest showed numerous deposits of birefringent calcium oxalate crystals in trabecular bone (Figure 4). The patient's only sibling in the United States, a 52-year-old sister, recalled two episodes of urolithiasis that resolved spontaneously. Her 24-hour urinary oxalate level of 2.5 mmol (222 mg) (normal, <0.5 mmol [<45 mg]) and 24-hour urinary glycolate level of 3.6 mmol (268 mg) (upper limit of normal, 1.1 mmol [or 81 mg])[15] confirmed the presence of type I primary hyperoxaluria. This sister declined all efforts to evaluate and maintain renal function but remains well. The children and the four other siblings had normal renal function and 24-hour urinary oxalate levels.

As results accumulated, the patient returned to work and consumed a low-oxalate diet supplemented with pyridoxine, 300 mg daily. Anemia responded to the intravenous administration of erythropoietin and oral iron and folic acid supplements. In March 1991, metacarpal, metatarsal, and forearm bone pain, which was radiographically negative, prompted a progressive increase in the duration and frequency of high-efficiency hemodialysis (using a blood flow rate of 350 ml per minute and a 1.8-m^2 surface-area, polysulfone hollow-fiber dialyzer) that gradually relieved the bone pain. All symptoms other than minor hand pain resolved during high-flux dialysis for 3.5 hours a day and 5 days a week throughout May and June until combined hepatic and renal transplantation at the University of California, Los Angeles, Medical Center in July 1991. The absence of function of the liver transplant led to a second orthotopic liver transplantation the next day. Intensive dialysis continued during the first ten postoperative days before acute tubular necrosis of the cadaveric renal transplant resolved. A low-oxalate diet, 5 liters of daily fluid intake, and magnesium citrate supplementation (28 mEq 3 times a day) allowed continued urinary excretion of the previously accumulated oxalate burden (Figure 5) without calculus formation or renal allograft oxalate deposition. Comparison of results of CT and nephrosonographic studies obtained soon after the appearance of end-stage renal failure and again 14 to 18 months after transplantation revealed notable mobilization of calcium oxalate from native renal cortices (see Figure 2).

In June 1995, the serum creatinine level was a mean 177 μmol per liter (2.0 mg per dl). Hepatic function remained normal during combined cyclosporine-prednisone immunosuppression treatment, and the patient was clinically well.

Comment

Subtle symptoms and signs of urolithiasis preceded end-stage renal failure in a middle-aged man by four years and were recognized only in retrospect. Renal biopsy led to the correct diagnosis. Evidence of oxalosis in a bone biopsy specimen and the results of renal imaging studies supported the diagnosis of primary hyperoxaluria type I. Confirmation followed the diagnosis of the disorder in a sibling. The rapid evolution of symptoms of oxalosis while the patient received pyridoxine and conventional dialysis prompted successful symptom reversal by intensive high-flux hemodialysis and combined hepatic and renal transplantation. The removal of

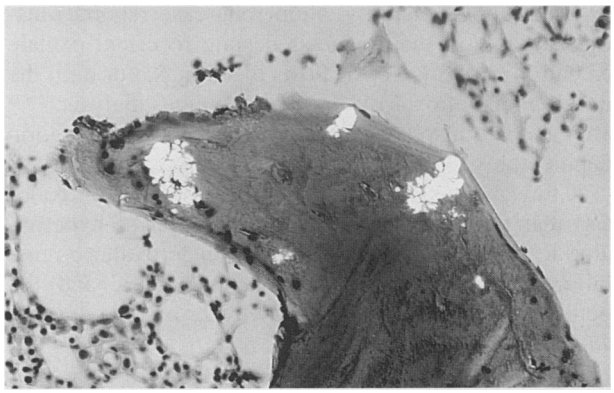

Figure 4.—An iliac bone biopsy specimen shows birefringent rosettes of calcium oxalate in trabeculae (hematoxylin-eosin stain; partially polarized light; original magnification, ×200).

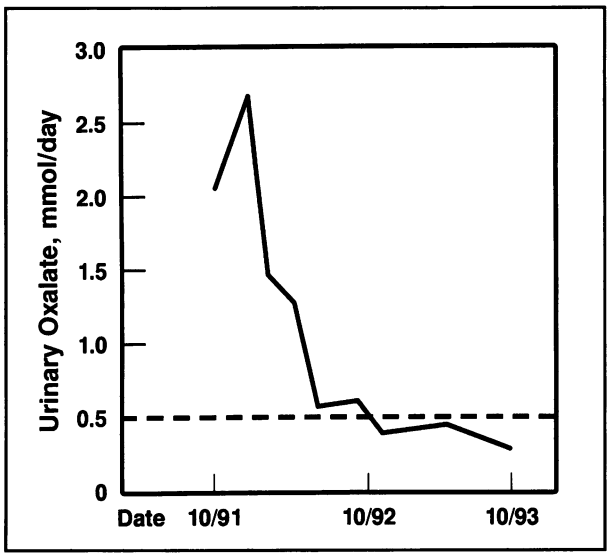

Figure 5.—The graph shows the patient's urinary oxalate excretion after transplantation. The broken line indicates the upper limit of normal (0.5 mmol/day).

oxalate in tissue required almost 1.5 years after the restoration of renal excretory capacity. Imaging study evidence of the dissolution of calcium oxalate in the renal cortex presumably mirrors dissolution in other sites, such as bone.

The early recognition of hyperoxaluria should receive major emphasis. Prompt detection and appropriate management of type I hyperoxaluria may prevent disabling consequences of oxalosis or the need for more elaborate therapy. If this patient had been referred to a nephrologist in April 1988, when renal function declined to 70% of normal, hyperoxaluria might have been considered as the cause of the episodic dysuria and microhematuria and of the incidental oxalate crystalluria. Considering the diagnosis of primary hyperoxaluria is the first obstacle. Obtaining expert guidance and confirming studies may present another problem.[11] Because this disorder is rare, few laboratories do reliable assays of plasma oxalate, plasma and urinary glycolate, or hepatic AGT activity. Numerous case reports illustrate a delay in the diagnosis despite recurrent oxalate calculi in childhood or oxalosis in siblings,[11] or until the development of oxalosis during continuous dialysis,[10,16-18] after renal transplantation,[19] or after pretransplantation nephrectomy.[20]

Clinical clues (including the manifestations of oxalosis) that should prompt the consideration of hyperoxaluria, the pathogenesis of chronic hyperoxaluric renal failure, diagnostic confirmation procedures, and the optimal management of primary hyperoxaluria are discussed next.

Recognition

Clinical indicators of type I primary hyperoxaluria include recurrent calcium oxalate urolithiasis, the most common indicator, tubulointerstitial nephropathy with nephrocalcinosis, which is a less frequent indicator, and eventually, symptomatic oxalosis.

Calcium Oxalate Urolithiasis

Because even a marginal elevation in urinary oxalate concentration promotes much greater supersaturation of calcium oxalate than similar increases in urinary calcium levels do, many advise measuring 24-hour urinary oxalate excretion in all patients with calcium oxalate calculi and certainly if calculi recur despite prophylaxis.[21] This policy ensures the identification of the rare patient with this disorder who presents with urolithiasis as an adult. The development of urolithiasis early in life characterizes primary hyperoxaluria. Factors that delay its initial manifestation until adulthood are poorly understood. The clinical investigation of renal insufficiency in an adult with evidence of diffuse cortical nephrocalcinosis or radiopaque calculi or a personal or family history of calcium-containing calculi in childhood should include measuring 24-hour urinary oxalate excretion. The diagnosis of primary hyperoxaluria should prompt the screening of all siblings—and possibly parents and children—for this recessive disorder. Heterozygous relatives excrete oxalate at rates observed in the normal population.

Urinalysis

Textbooks of laboratory diagnosis have commented on the frequent, incidental presence of bipyramidal (octahedral) calcium oxalate dihydrate crystalluria in normal persons, which excludes using the results of urinary sediment examination to predict hyperoxaluria.[1] In the case reported here, however, the notation of "4+ calcium oxalate crystals" on each of four otherwise routine urinalysis reports during ten years, when the serum creatinine level rose from 88 μmol per liter (1 mg per dl) to 124 μmol per liter (1.4 mg per dl), might have prompted a 24-hour urine oxalate determination and a review of the renal ultrasound study for signs of early nephrocalcinosis.

Tubulointerstitial Nephropathy–Nephrocalcinosis

Clinical or histologic evidence of a tubulointerstitial process of unknown cause should indicate the possibili-

TABLE 2.—*Features of Unexplained Renal Insufficiency or Failure Suggesting Primary Hyperoxaluria Type I (PH-I)*

Family history of PH-I or oxalosis
Personal or family history of calcium oxalate urolithiasis, especially in childhood
Cortical nephrocalcinosis with or without radiodense calculi
Any clinical manifestation of oxalosis, especially if confirmed by biopsy specimen examination
Bone or renal histologic examination shows more extensive oxalate deposition than anticipated in patients with non–PH-I ESRF
A reliable plasma oxalate level elevated beyond that expected in ESRF unrelated to PH-I

ESRF = end-stage renal failure

TABLE 3.—*Location and Clinical Manifestations of Oxalosis*

Tissue	*Clinical Manifestations*	*Supportive Study*	*Reference*
Bone, bone marrow	Osseous pain, spontaneous fracture, erythropoietin, resistance, pancytopenia, myelofibrosis, hypercalcemia, progressive edentia	Skeletal x-ray film, radioisotopic bone scan, bone biopsy	Canavese et al, 1990[16]; Breed et al, 1981[17]; Noël et al, 1989[19]; Day et al, 1986[22]; Toussaint et al, 1993[25]; Mathews et al, 1979[26]; Absy et al, 1991[27]; Moskow, 1989[28]
Synovium, tendon, cartilage	Acute and chronic arthropathy, chondrocalcinosis, bursitis, tendinitis	X-ray film, arthrocentesis, synovial fluid analysis, synovial biopsy	Verbruggen et al, 1989[14]; Moskow, 1989[28]; Hoffman et al, 1982[29]; Reginato et al, 1986[30]
Arteries, arterioles	Vasospasm, acrocyanosis, livedo reticularis, claudication, gangrene, angioaccess occlusion, vascular calcification	X-ray films, dermal biopsy, muscle biopsy	Watts et al, 1991[2]; Kay, 1993[11]; McDonald et al, 1989[20]; Day et al, 1986[22]; Winship et al, 1991[31]; Spiers et al, 1990[32]
Skin	Subcutaneous calcinotic nodules or masses, occasionally ulcerating	X-ray films, dermal biopsy	Day et al, 1986[22]; Moskow, 1989[28]; Scheinman et al, 1984[33]
Myocardium	Conduction defects, ventricular tachyarrhythmias, cardiomyopathy	Electrocardiogram, myocardial biopsy	Watts et al, 1991[2]; Kay, 1993[11]; Koten et al, 1965[13]; McDonald et al, 1989[20]; Absy, 1991[27]; Spiers et al, 1990[32]; Walls et al, 1969[34]
Retina	Mildly diminished vision, crystalline maculopathy	Ophthalmoscopy	Small et al, 1992[35]
Nervous system	Dysesthesia, weakness, symmetrical polyneuropathy, mononeuritis multiplex, optic atrophy	Peripheral nerve biopsy, ophthalmoscopy	Watts et al, 1991[2]; Scheinman et al, 1984[33]; Boquist et al, 1973[36]; Moorhead et al, 1975[37]

ty of primary hyperoxaluria type I if a patient has a history of calcium urolithiasis, nephrocalcinosis, or birefringent crystalline deposits in biopsy specimens. The results of urine protein electrophoresis in this patient suggested tubulointerstitial nephropathy, which was confirmed by renal biopsy.

The classic imaging feature of long-standing primary hyperoxaluria is diffuse cortical nephrocalcinosis with or without radiodense urinary tract calculi.[22,23] This finding is simulated only infrequently by the recovery from acute renal cortical necrosis, or rarely by chronic glomerulonephritis or sustained hypercalcemia, but the cortical calcifications are usually more linear or punctate than in primary hyperoxaluria, in which cortical density is diffuse.[23,24]

The clinical features of chronic renal insufficiency or failure that signal the presence of primary hyperoxaluria are listed in Table 2.

Oxalosis

Clinical manifestations of oxalosis (Table 3),* most frequent in bone, arteries, myocardium, skin, and synovia, may signal the presence of primary hyperoxaluria. The many case reports of patients with one or more frequently disabling manifestations of oxalosis attest to the importance of alertness to the possible clinical consequences of oxalate deposition in tissue. In primary hyperoxaluria, the varied findings of oxalosis were common before dialysis became available but are noted today—primarily in patients who enter renal failure with the condition undiagnosed or who receive standard dialysis.

In patients with progressive renal insufficiency unrelated to primary hyperoxaluria, the oxalate miscible pool and plasma levels are only mildly elevated even at a GFR of 8 to 10 ml per minute.[5-7,38] Tissue oxalate accumulation remains limited.[5] Conventional peritoneal dialysis and hemodialysis remove most normally generated oxalate if ascorbic acid supplements are limited to 100 mg daily.[6,39,40] Oxalosis associated with long-term dialytic therapy for renal failure from nonoxalotic causes tends to be an incidental histologic finding despite distinctly elevated plasma oxalate levels (15 to 18 times normal).[5-7,41] When clinically apparent in these patients, oxalate-induced synovitis,[29,30] cutaneous calcinosis,[30,42] oxalate osteopathy,[43] or complete heart block[41] are usually associated with prolonged dialysis (5 to 23 years), ascorbic acid supplementation (300 to 2,600 mg a day), high oxalate intake, or a combination of these factors.

Biopsy

Identifying birefringent calcium oxalate crystals in synovial fluid,[29,30] in myocardial tissue,[11,32] in the tunica media of arteries and arterioles, or occluding the lumina of small blood vessels on examination of biopsy speci-

*References 2, 11, 13, 14, 16, 17, 19, 20, 22, 25-37.

mens of specific tissues—skin and subcutaneous tissue,[11,31,32] muscle,[20] peripheral nerve,[37] synovium[29]—suggests the correct diagnosis of primary hyperoxaluria type I in patients who have end-stage renal failure of unknown cause. The longer the duration of renal failure before appropriate tissue is obtained through biopsy, the more pronounced is the histologic oxalosis.

Because the deposition of calcium oxalate crystals in trabecular bone is prominent in patients with primary hyperoxaluria in whom severe renal insufficiency is developing, the examination of percutaneous trephine bone biopsy specimens should suggest the correct diagnosis.[26] In contrast, the examination of an aspiration bone marrow biopsy specimen did not reveal oxalate deposition in a patient with the classic findings of oxalate-induced granulomatous myelofibrosis on examination of a later, formal bone biopsy specimen.[27] Others have noted the futility of examining aspiration bone marrow biopsy specimens in establishing the diagnosis of oxalosis.[36,44,45]

The efficacy of the examination of a renal biopsy specimen to diagnose this disorder as a cause of chronic renal insufficiency has not been documented. In the absence of superimposed oliguria, the biopsy specimen may reveal tubulointerstitial nephropathy without prominent oxalate crystal deposition. After dialysis is initiated in patients with end-stage renal failure, however, histologic examination of formalin-fixed, hematoxylin- and eosin-stained specimens of kidney should show large amounts of birefringent crystals within tubules.[33] Reflecting sustained overproduction and extremely high plasma levels of oxalate, the progressive deposition of calcium oxalate in these hypoperfused kidneys exceeds that incidentally noted in renal failure from other causes.[46] As shown by this patient, histologic evidence of renal oxalate deposition may be relatively minor in some patients with primary hyperoxaluria type I soon after the evolution of end-stage renal failure despite massive diffuse infiltration of the cortex by a form of calcium oxalate that is not doubly refractile on polarizing microscope examination. This situation may be clarified by considering the pathogenesis of chronic oxalate nephropathy.

Pathogenesis of Renal Failure in Primary Hyperoxaluria Type I

Possible mechanisms of renal injury in hyperoxaluria type I uncomplicated by calculous obstruction and pyelonephritis include crystalline obstruction of renal tubules, a rising level of plasma oxalate that complexes with the relatively concentrated intracellular calcium in renal tissue, or a toxic effect of hyperoxaluria on renal tubular epithelium.

The subtle intrarenal calcium oxalate precipitation in this patient is like that described in many patients with acute or chronic renal failure of any cause[41,47] and is dissimilar to the often-reported massive deposition in crystalline-occluded cortical convoluted tubules.[1,34,36] When clinical details are provided, proximal tubular obstruction by calcium oxalate rosettes in patients with this disorder accompanies acute neonatal renal failure,[44] dehydration and oliguria in children and adults,[12,13] or long-term dialysis with abundant evidence of systemic oxalosis.[34,36] Acute oliguria associated with contraction of the extracellular fluid volume or hypotension may allow the intratubular crystallization of calcium oxalate and may precipitate acute renal decompensation.

The chronic renal insufficiency in patients with sustained hyperoxaluria may be engendered by direct crystalline injury to renal tubular epithelium, initiating interstitial inflammation, giant cell formation, fibrosis, and nephrocalcinosis. The experimental production of mild chronic hyperoxaluria or moderate acute hyperoxaluria injures renal tubular epithelial cells in rats.[48] The absence or limited evidence of oxalate deposition despite interstitial nephritis has been documented in patients with primary hyperoxaluria type I before clinically important azotemia developed.[34,45,49] Light or electron microscopy has shown that intratubular crystals invade tubular cells and the interstitium, inducing patchy epithelial proliferation and interstitial inflammation.[36,50] Much less intraluminal oxalate crystal deposition has been noted in pyelonephritic kidneys than in noninfected, "nonobstructed," but anuric contralateral kidneys in two adult patients with type I hyperoxaluria who were dying of uremia.[13] This finding suggests that sustained diuresis and natriuresis of residual nephrons inhibit the intratubular precipitation of oxalate otherwise expected with extreme elevation of the plasma oxalate level.[45] Progressive deterioration of renal transplant function unrelated to rejection in patients with this disorder with only modest oxalate accumulation on the examination of specimens from serial renal biopsies suggests a direct toxic effect of massive hyperoxaluria in the initial months after transplantation.[33] Linear deposition of antitubular basement membrane antibody, severe tubulointerstitial nephropathy, and extensive intrarenal deposition of oxalate in a patient with enteric hyperoxaluria implicated oxalate damage to tubular epithelium, the release of tubular antigens, and immunologically mediated interstitial nephritis as the mechanism of renal failure in a 38-year-old patient 18 months after jejunoileal bypass.[51] Similar immunologic evidence is missing in patients with type I primary hyperoxaluria.

Diagnosis

Establishing the diagnosis of this disorder requires the demonstration of prominently elevated urinary or plasma levels of oxalate and evidence of an overproduction of glycolic acid, hepatic biopsy specimen documentation of deficient or mistargeted AGT, or in an appropriate setting (such as patients with nephrocalcinotic end-stage renal failure, biopsy evidence of oxalosis, or the exclusion of other hyperoxaluric causes), the confirmation of the disorder in a sibling (Table 4). Generally accepted values for oxalate and glycolate in various clinical circumstances reflect the results of sensitive assays done specifically to exclude interfering sub-

TABLE 4.—*Confirmation of Primary Hyperoxaluria Type I (PH-I) in End-Stage Renal Failure (ESRF)*

Hepatic biopsy—absent or severely deficient AGT activity; AGT maldistribution
Elevated plasma glycolate
With other features of PH-I–induced ESRF, hyperoxaluria, and glycolic-aciduria in a sibling

AGT = alanine-glyoxylate aminotransferase

stances such as ascorbic acid. Table 5 lists some of the laboratories that perform many of these special tests. The precise collection and handling of specimens is critical for reliable results.[3,6,38,52]

With adequate renal function, normal levels of urinary oxalate (<0.5 mmol [45 mg] per 1.73 m^2 in 24 hours) readily exclude the presence of primary hyperoxaluria. Patients with type I hyperoxaluria rarely have 24-hour oxalate excretion levels of less than 1.1 mmol (100 mg) per 1.73 m^2; mean excretory rates are 2.7 mmol (240 mg) and exceed 4.4 mmol (400 mg) in a few patients.[1,45] Acidifying 24-hour urine specimens during collection to a pH of less than 2.0 (by adding 20 ml of concentrated hydrochloric acid to the collection bottle) is mandatory to prevent the precipitation of oxalate salts and to limit the spontaneous nonenzymatic conversion of urinary ascorbate to oxalate.[3,52,53] If 24-hour urine collection proves impossible, simultaneous oxalate and creatinine determination by using a fasting second-voided morning urine specimen should allow the diagnosis of type I primary hyperoxaluria to be suspected or excluded.[54] A urinary oxalate:creatinine ratio exceeding 0.06 mmol:mmol (0.05 mg:mg) is characteristic of older children and adults with this disorder (most values exceed 0.125 mmol:mmol or 0.1 mg:mg).[3,15]

With mildly to moderately reduced renal function, patients continue to excrete oxalate in amounts approximating their high generation rates—1.2 to 4.5 mmol (108 to 405 mg) in 24 hours—have oxalate clearance as high as 2.7 times the corresponding creatinine clearance (implying clinically important proximal tubular secretion of the anion), and have a plasma oxalate level four to five times that of normal persons.[7,55] Urinary oxalate excretion progressively diminishes with GFRs of less than 40 ml per minute, but may remain sufficiently elevated to permit a suspicion of primary hyperoxaluria in patients with even moderately severe renal insufficiency. Limited glomerular filtration and tubular secretory capacity in renal failure prevent oxalate excretion determination from assisting in the diagnosis of the disorder with end-stage renal failure. Because plasma oxalate levels in these patients rise asymptotically with a decline in GFRs to less than 40 ml per minute, and particularly to less than 25 ml per minute, plasma oxalate and plasma oxalate:creatinine ratios are appreciably higher than they are in patients with similar degrees of chronic renal dysfunction unrelated to hyperoxaluria.[5-7,38,55]

In at least 75% of patients, an elevated 24-hour urinary glycolate level and especially a 24-hour urinary glycolate:creatinine ratio confirm the presence of primary hyperoxaluria type I.[1,4,5,15] A dramatically elevated plasma glycolate level in renal failure is present only in patients with this disorder.[38] A substantial decline in glycolate values with vitamin B_6 treatment confirms the presence of pyridoxine-responsive type I primary hyperoxaluria.

Patients with this disorder without evidence of excessive glycolate generation may require assays of hepatic AGT activity and subcellular location, the study of siblings, the repeated demonstration of reduced oxalate generation with pyridoxine supplementation, the exclusion of other causes of hyperoxaluria, or some combination of these methods to confirm the diagnosis.

Non-Type I Primary Hyperoxaluria

Excluding alternative causes of hyperoxaluria (Table 6) is usually straightforward. All are proven or possible contributors to oxalate urolithiasis; five must be considered in the differential diagnosis of oxalate nephropathy. Rare type II hyperoxaluria, documented in about 22 patients since 1968,[56] can be diagnosed by verifying excessive oxalate production and elevated urinary or plasma levels of L-glyceric acid or deficient activity of D-glycerate dehydrogenase in peripheral leukocytes or hepatic biopsy tissue. Urinary glycolate levels are normal or low in patients with type II primary hyperox-

TABLE 5.—*Laboratories Willing to Do Diagnostic Studies on Special Request*

Name, Address, and Telephone No. of Laboratory	*Assay*
D. A. Applegarth, PhD Biochemical Diseases Laboratory Dept of Pathology British Columbia Children's Hospital 4480 Oak St Vancouver, BC V6H3V4 (604) 875-2307	Hepatic biopsy: assay of AGT activity
Marguerite Hatch, PhD Div of Nephrology C 351, Med Sci 1 University of California Irvine, CA 92717 (714) 856-5562	Urinary and plasma oxalate
G. P. Kasidas, PhD Dept of Clinical Pathology University College and Middlesex School of Medicine Windeyer Bldg Cleveland St London W1P 6DP United Kingdom 071-636-8333	Hepatic biopsy: assay of AGT activity and subcellular location
Hibbard E. Williams, MD Office of the Dean, School of Medicine University of California Davis, CA 95616 (916) 752-0321	Urinary glycolate
David M. Wilson, MD Mayo Medical Laboratories Mayo Clinic Rochester, MN 55905 (507) 284-3019	Urinary and plasma oxalate, urinary and (?) plasma glycolate, and urinary L-glycerate

AGT = alanine-glyoxylate aminotransferase

TABLE 6.—*Differential Diagnosis of Hyperoxaluria*

Type	*Cause*
Primary hyperoxaluria	
Type I	AGT deficiency*
Type II	D-Glycerate dehydrogenase deficiency*
Type III	Hyperabsorptive
Secondary hyperoxaluria	Excessive oxalate intake
	Enteric hyperoxaluria*
	Ethylene glycol ingestion*
	Prostatectomy glycine irrigation
	Aspergillus species infection*
	Methoxyflurane anesthesia*
	Xylitol infusion*
	Piridoxilate therapy*
	Pyridoxine deficiency
	?Excessive ascorbic acid intake

AGT = alanine-glyoxylate aminotransferase

*Documented cause of oxalate nephropathy.

aluria. Hyperabsorptive type III hyperoxaluria reflects primary excessive intestinal absorption of divalent cations and oxalate without the recognizable structural features of the secondary forms of enteric hyperoxaluria. It responds to dietary oxalate restriction and long-term thiazide diuretic treatment.[57]

High dietary intake of oxalate in rhubarb, spinach, beet, parsley, pepper, peanut, chocolate, cocoa, and tea increases oxalate excretion and the risk of oxalate calculus formation.[52] Acute nephropathy accompanying oxalate poisoning from the ingestion of plants appears primarily ischemic.[58] Enteric hyperoxaluria from small intestinal disease, bypass surgery, or resection; chronic pancreatic or biliary tract disease; or complexing of dietary calcium by cellulose phosphate has caused calcium oxalate urolithiasis and oxalate-induced renal insufficiency.[51,53] Ethylene glycol remains a clinically important cause of acute oxalate nephropathy. Glycine absorption from the prostatic bed during transurethral prostatectomy occasionally induces clinically notable oxaluria.[59] The production of oxalic acid by severe infection with *Aspergillus* species has induced acute renal insufficiency histologically consistent with oxalate nephropathy.[60] Although methoxyflurane and xylitol cause hyperoxaluria, these compounds are no longer clinically available. Another hyperoxaluric agent, the vasodilator piridoxilate, has never been released in the United States.[61] Although proved experimentally, pyridoxine deficiency has not been clinically proved to cause substantial hyperoxaluria.[1,53,61] Megadoses of ascorbic acid may lead to laboratory evidence of hyperoxaluria.[52] Recent research in which the nonenzymatic conversion of urinary ascorbic acid to oxalate was controlled for and that used ion chromatography to accurately measure urinary oxalate excretion suggests that a supplementary dosage of oral vitamin C as high as 10 grams daily does not increase the urinary excretion of oxalate in normal subjects.[62]

Management

Pyridoxine Supplementation

Every patient should receive a therapeutic trial of pyridoxine during which urinary oxalate level, glycolate level, or both should be monitored (plasma glycolate level should be monitored if substantial renal impairment exists) (Table 7).[15,38,63] In patients with pyridoxine-responsive variants of type I hyperoxaluria, pyridoxine treatment often reduces the oxalate and glycolate levels to normal. Even a partial response benefits patients by limiting oxalate production through enhanced conversion of glyoxylate to glycine. Pyridoxine supplementation may elevate aminotransferase apoenzyme levels or may enhance the binding of vitamin B_6 to variants of AGT with low affinity for this essential cofactor.[9] Only a few patients with primary hyperoxaluria type I are sensitive to pyridoxine, however (7% in one series).[4] Although pharmacologic doses of 200 to 2,000 mg a day have been well tolerated,[8,19] severe sensory neuropathy within months of initiating vitamin B_6 supplementation mandates monitoring deep tendon reflexes and position and vibration senses.[64]

Preventing Urinary Oxalate Crystallization and Urolithiasis

Patients unresponsive to pyridoxine must adhere strictly to a program designed to allow maximal renal clearance of oxalate in as soluble a form as possible.[33] This program requires producing high daily volumes of diluted urine (which reduces the concentration and supersaturation of urinary calcium oxalate); avoiding extracellular fluid volume contraction, prostaglandin-inhibiting anti-inflammatory agents, and possible nephrotoxins[65,66]; and consuming inhibitors of urine calcium oxalate crystallization. With adequate renal function, adult daily doses of orthophosphate, 30 to 35 mg per kg of body weight[53,67]; magnesium oxide, 450 mg[53,63]; or sodium or potassium citrate, 40 to 60 mEq,[68,69] limited calcium oxalate urinary supersaturation, calculus formation, and at least for orthophosphate, renal insufficiency.[67] To minimize the incidence of diarrhea, initially small divided doses taken with meals are progressively increased to recommended levels. The patient in this report tolerated post-transplantation daily doses of 1 gram of magnesium and 84 mEq of citrate (as magnesium citrate) without side effects during the 17 months before urinary oxalate levels returned to normal. Serum magnesium levels remained normal. Percutaneous renal transplant biopsy at seven weeks disclosed a scant amount of oxalate proportional to the degree of renal insufficiency (serum creatinine level, 265 μmol per liter [3.0 mg per dl]). Renal biopsy 18 months after transplantation showed no evidence of oxalate crystals.

Although dietary oxalate provides a small fraction of the oxalate generated endogenously in patients with type I hyperoxaluria, such patients should avoid high-oxalate foods and ascorbic acid supplementation. Calcium intake should not be excessive. Because dietary calcium

TABLE 7.—*Management of Adult Patients With Primary Hyperoxaluria Type I*

Variable	Treatment
GFR ≥40 ml/minute	Pyridoxine trial
	High fluid intake; urine output >3 liters/day
	Crystallization inhibitors
	Neutral orthophosphate
	Magnesium
	Citrate
	Thiazide diuretic if patient has hypercalciuria
	Normal calcium level, low-oxalate diet without ascorbic acid supplements
	Avoid dehydration, possible nephrotoxins
	Prompt relief of urinary tract obstruction or infection
	Monitor renal function frequently
GFR <40 ml/minute	Continue measures listed above*
	Monitor renal function and plasma oxalate levels closely
	When GFR is 20-25 ml/minute, consider elective transplantation
	Initiate intensive hemodialysis when early ESRF results in systemic oxalate accumulation and before transplantation
	Avoid nephrectomy before ESRF

ESRF = end-stage renal failure, GFR = glomerular filtration rate

*Orthophosphate and magnesium are contraindicated.

forms complexes with gastrointestinal oxalate, which limits its absorption, documented hypercalciuria should be controlled by a thiazide diuretic instead of restricting calcium consumption below normal.[21,33] Caution is advised because of the capacity of thiazide diuretics to reduce the renal excretion of oxalate indirectly by contracting extracellular fluid volume and directly by inhibiting the tubular secretion of oxalate.[54] The optimal management of urinary calculi or infection includes a prompt recognition and use of kidney-preserving endoscopic and lithotriptic techniques and of non-nephrotoxic antibiotic agents. Extracorporeal shock-wave lithotripsy is relatively contraindicated.[70]

Preventing and Treating Oxalosis

The avoidance of disabling, possibly fatal oxalosis mandates close monitoring of renal function and considering transplantation before declining GFRs accelerate the systemic deposition of oxalate. Recent articles document arguments for various transplantation strategies: renal,[71] orthotopic hepatic,[72] and sequential[20] or simultaneous[2,10] orthotopic hepatic and renal transplantation. Heterotopic, auxiliary hepatic transplantation would not limit the excessive generation of oxalate by the native AGT-deficient liver.[10]

As demonstrated in this case and other reports, prolonged and frequent (even daily) hemodiafiltration or hemodialysis using high-flux membranes and blood flow has proved superior to conventional hemodialysis and peritoneal dialysis when dialytic support is required to limit oxalate accumulation and to deplete oxalate stores before transplantation.[7,40,63,73] The clearance of oxalate with a polysulfone or polyacrylonitrile membrane dialyzer averages 40% higher than the 82-to-89-ml-per-minute clearances produced by cellulosic membrane dialyzers of conventional size at the standard blood flow.[40,63] High-flux dialysis with the type of dialyzer used in the case described here produces oxalate clearance of about 180 ml per minute.[73] Because continuous ambulatory peritoneal dialysis and standard hemodialysis remove a mean 30% of the oxalate generated in primary hyperoxaluria type I, their sustained use is not recommended.[6,16,63] The longer the duration of conventional dialysis, the greater the oxalate burden and the less favorable the outcome of renal transplantation because of superimposed transplant oxalate nephropathy.[33]

The restoration of renal function by successful transplantation, followed by the provision of inhibitors of urinary calcium oxalate precipitation and by high fluid intake, permits the sustained clearance of accumulated oxalate.[33,71] The patient described in this review had urinary oxalate excretion as high as five to six times the upper limit of normal before levels returned to normal 17 months after transplantation. As the miscible oxalate pool is reduced, the dissolution of tissue oxalate resolves many manifestations of oxalosis: osteodystrophy,[10,22,25] complete heart block and cardiomyopathy,[2,20] neuropathy,[2] and cutaneous and subcutaneous deposits.[33] Imaging studies in this case document the mobilization of native renal cortical calcium oxalate deposits after the enzyme deficiency was corrected and adequate renal function was restored.

The diverse spectrum of acuity and age at onset of type I hyperoxaluria does not seem to be correlated with variations in AGT activity and subcellular location or the magnitude of hyperoxaluria.[4,18,45,71] To recognize the disorder early and initiate prophylaxis to reduce oxalate generation in some patients and provide optimal oxalate clearance in all patients remain the primary goals. Although intensive hemodialysis or renal or hepatic transplantation may prove optimal for selected patients in whom end-stage renal failure develops, combined hepatic and renal transplantation offers the best chance for cure. Improved inhibitors of urinary crystal growth, intestinal oxalate-complexing agents, and hepatic AGT gene transfer hold promise as future treatment methods.

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